Elucidating the Pathogenesis and Rx of COVID Reveals a Missing Element

ABSTRACT

This article is based on a KZN doctor's experiences of treating COVID patients in an outpatient setting. His broad natural science background has afforded him a unique perspective of the pandemic, convincing him that something was missing. From the examination, treatment and follow up of over 200 symptomatic COVID patients, it is his opinion that COVID illness has two aetiologies, namely an initial respiratory viral infection with typical symptoms, progression and outcomes and a later triggering of a Type 1 hypersensitivity reaction in those that are sensitive. This article looks at the pathogenesis of COVID and his outpatient treatment protocols

Currently there are few outpatient treatment recommendations, and there is a distinct lack of understanding of the disease progression. This is most likely due to the absence of sufficient outpatient examination, treatment and follow up because of isolation measures and current protocols. There is however a wealth of information around hospital presentations, investigations and pathological findings. Hospital treatment protocols are based on these findings, but have thus far not been universally consistent in efficacy and outcome. This has created controversy and confusion as to the pathogenesis and treatment of COVID.

Over the past five months, my staff and I have examined, treated and followed up on over 200 symptomatic COVID patients, some critically ill. In doing so, I used the information gathered to refine my understanding of the pathogenesis of COVID and thus adjust treatment protocols.

This has resulted in some remarkable yet consistent and predictable results and recoveries. In all, we have had no deaths, no hospitalisations and complete recoveries of all patients, even those with severe dyspnoea. Most confirmatory to my theory of the pathogenesis were the 12 most dyspnoeic patients with low 80% SpO_2 that recovered to over 96% SpO_2 within 24 to 36 hours of treatment, without the need for hospitalisation or oxygen. All dyspnoeic patients had normal SpO_2 within 3 days of treatment.

The information thus gathered can prevent most of the mortality and morbidity from COVID. The furthering of understanding of the pathogenesis of COVID can guide future research and intervention strategies to negate the effects of the pandemic.

Virus, detection and symptoms

A RNA virus

Airborne transmission. Common in stool samples? Waterborne transmission. The virus is highly contagious but infectivity and virulence are unknown due to a lack of understanding of the pathogenesis of COVID and testing limitations.

The virus enters the cell through ACE 2 receptors. Like other common RNA viruses, it uses cell machinery to replicate and burst out copies, leaving behind dead cell debris and inflammation that could result in mild scarring. The average duration of symptoms is 3 to 6 days with the host being non-infective after day 7.

Laboratory detection

Swabs vary greatly in their ability to isolate the virus due to technique used, training of screeners, the area swabbed etc. PCR tests are very specific but not very sensitive - about 65%, so about 35% false negatives - and so cannot be used for diagnosis or confirmation of diagnosis. It is only useful for screening purposes but not sensitive enough to guide detection and isolation/quarantine measures. Absolute numerical data is not a true reflection; ratios may yield a better insight Antibody testing may provide more reliable data.

Clinical presentation based on personal observations

- Infection of upper respiratory tract - sore throat, loss of smell, loss of sweet and salty taste, bitter preserved. Generalised body ache, fever with chills.
- Spreads lower - dry persistent cough, cold feeling between shoulder blades, burning sensation in chest, tightness with scanty, clear sputum.
- Bacterial co-infection - productive cough with purulent sputum, sinusitis with purulent mucus, earache etc. The above symptoms are progressive over the first 6 days of infection and may

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lead to a pneumonia with associated dyspnoea.

- A significant proportion of infected symptomatic individuals develop dyspnoea from day 7 onwards, irrespective of severity or duration of initial symptoms. Common associated symptoms are mild generalised body pain and fatigue to the point of having to sleep. This dyspnoea can be of sudden onset and rapidly progressive, leading to severe hypoxaemia and a SpO2 drop to below 85% in 2 days. It is more commonly insidious in onset and persistent for a variable duration, with SpO2 in the mid to low 90s, and may result in diffuse lung fibrosis the longer it persists. It is during this period that the rashes, neurologic symptoms and end organ damage are also reported.
- Gastrointestinal infection is common - usually preceded by a sore throat that spontaneously resolves in a day or two, heartburn, nausea, short severe intermittent abdominal cramps with tinkles and gurgling, severe diarrhoea that slows to a poorly formed, sometimes slimy stool in 4 to 5 days.
- Other reported symptoms - conjunctivitis, a variety of skin rashes, distal ischemic digit injuries, varied neurologic symptoms, symptoms of organ injury or failure.

Case morphology

Understanding the progression of this illness also requires an overview of the facts as they currently are occurring, compared to the facts as they are known to be.

Known facts

Viruses are generally quite specific in the type of tissue they infect. Their infections are generally self-limiting, opportunistic and seldom cause death. Mortality is usually due to some other predisposition, either natural or chronic illness related.

Respiratory viruses cause symptoms ranging from none (most), to a mild sore throat which passes in a few days, or spreads lower, and can complicate with a bacterial infection ranging from mild bronchitis to pneumonia, with typical radiologic findings. These symptoms are progressive and well understood, and these typical case presentations should be removed from analysis, to help concentrate on what is unknown.

Facts as they are occurring

What remains are case histories that don't fit the profile mentioned above, are atypical for a single virus, and don't show typical disease progression and rates.

Unusual symptoms:

- Hypoxaemia poorly correlated to levels of dyspnoea. Sudden, rapidly progressive dyspnoea and SpO2 drop, in an otherwise healthy patient, resulting in poor outcomes.
- Slow chronic hypoxaemia with variable chronic lung damage from fibrosis over variable duration. Associated with a persistent, dry cough with or without wheezing.
- Mild SpO2 drop, not below 92% and may need intermittent oxygen. Usually resolves spontaneously in a few days to a week.
- Autopsy findings: Lungs are oedematous and heavy with microvascular clots. Multiple organ involvement usually due to hypoxic injury, DIC. Or, immune/inflammatory response rather than direct viral infection.
- Chronic manifestations: COPD, Kawasaki like illness in children, hypoxic injuries, thromboembolic injuries, diabetes.

Unusual outcomes:

If we remove the usual risk-factor related outcomes that may complicate a typical viral infection, we are left with poor age and health status correlation. Fit, healthy 25 year olds have succumbed suddenly, and high risk 90 year olds got through uneventfully. Patients with mild prolonged illness can present back in a few months with chronic disease, commonly COPD, and diabetes. Men are more at risk with multiple intra-family fatalities related to increased risk of infection and or genetic predisposition. Many father/son deaths have occurred with the mother being spared, and vice versa, but less commonly. Varying mortality rates between countries and ethnicities. Children below 10 years old are least at risk.

Pathogenesis from morphology

It is clear from the case morphology that a viral infection alone cannot explain the diversity of symptoms, unusual presentations and unusual outcomes. Taking an overview using the wealth of information available from the pathogenesis of a variety of conditions, may allow us to find the best fit for the unusual presentations and outcomes that are seen.

The only pathogenesis that fully explains these outcomes are Type 1 hypersensitivity reactions, the allergic reactions we have to external allergens, whether inhaled, ingested, or contacted. These reactions consist of an initial acute phase that lasts a few hours to a few days, and can be mild to fatal. They sometimes progress to a late phase reaction that lasts for a week or so, resulting in cell damage and other immune implications. Reactions to the same allergen vary in speed, severity, duration and symptoms, and if not treated, would have diverse outcomes, ranging from sudden anaphylactic type reactions leading to rapid deterioration and death, to moderate chronic allergic reactions resulting in scarring and collateral immune mediated injuries, to mild, transient, localised reactions.

In my opinion, and from my examination, treatment and review of over 200 COVID patients, the initial Corona virus infection is like any other common respiratory virus infection, with a spread of statistics in similar ratios to previous epidemics, during the initial 7 days. On around the 7th day, a Type 1 hypersensitivity reaction is triggered in the lungs, probably due to a recognisable viral protein fragment causing the release of chemical mediators, leading to the variety of presentations and outcomes that have been encountered, including chronicity and complications due to non-treatment. This reaction would not be directly related to age, comorbidities etc., but directly related to genetic predisposition and immune maturity, or lack thereof.

It may explain the sudden deterioration in lung oxygen exchange capacity and SpO_2, in the asymptomatic and mild transient viral illness, at around the 7th day. The speed of deterioration varies greatly and can complicate an otherwise uneventful recovery of a high risk patient post day 7.

Those that have severe initial Type 1 reactions, presenting with sudden onset dyspnoea with steadily declining SpO_2, can deteriorate rapidly and are at high risk of mortality. However, some with milder initial reactions that progress to late stage Type 1 hypersensitivity reactions present with persistent dry cough, symptoms of mild hypoxia or hypoxic injury etc, with mild but prolonged SpO_2 drop. These will have varying degrees of lung damage over time.

Many of the reported chronic manifestations of COVID are explained by immune injury to the lungs (cytokine response) and collateral immune or hypoxic injury to other organs or systems. The gastrointestinal symptoms are likely due to an initial viral gastroenteritis, followed by a prolonged allergic bowel inflammation and irritability, with chronic sequelae.

BCG vaccination and active PTB seem to modulate immunity and avert severe Type 1 reactions. Patients on immunomodulatory treatments are less likely to have a severe Type 1 reaction.

Children's underdeveloped immunity is less likely to trigger a Type 1 reaction. Generally, younger patients will have no reactions due to it being their first exposure to the allergen. A reaction requires previous exposure. They will however, become sensitised, and subsequent exposure can provoke a more vigorous immune response. Those with mild to moderate initial reactions will become more tolerant to subsequent exposures. They will however, consequently become passive future transmitters of the virus.

Seeing that reports of reinfections are surfacing, a Type 1 reaction may provide an explanation for a prolonged second wave of infections with higher mortality in the younger population (sensitised individuals), and a shorter third wave with generally low mortality (tolerance) as per the Spanish Flu.

Treatment toolbox

As I consider this disease to have two overlapping aetiologies, ie, viral and allergic, treatment would differ depending on the point at which it is initiated.

Outpatient drugs used so far

Hydroxychloroquine has been very controversial and has historic prophylactic use against viral infection, and has shown some prophylactic benefit in trials on healthcare workers. It has anti-inflammatory, antihistaminic, smooth muscle relaxant and antiarrhythmic properties. This could have symptomatic benefit during the viral phase of COVID illness. Its immunomodulatory effect would be of more benefit in the allergic reaction, but may be too slow in onset to be of benefit, if started well into the initial 7 days. The immunomodulatory effect of ivermectin may have a more rapid onset.

- Azithromycin has shown benefits in treating the usual and atypical bronchopneumonia complicating viral infections, and should be the antibiotic of choice in cases complicated by bacterial URTIs.
- Doxycycline has a wide range of effects, and through its inhibitory effects on protein synthesis, can potentially slow viral replication. This can potentially decrease symptom severity and infectivity of infected individuals.
- The viral phase of the illness is generally mild and self-limiting and symptomatic treatment would be sufficient in most.

Drugs to treat Type 1 hypersensitivity reactions

- Adrenaline is used to treat hypovolemic shock. It can also be used to nebulise patients with rapidly progressive reactions and severe dyspnoea.
- Prednisone is indicated to suppress any sudden onset severe allergic reaction. Its use from day 7 onwards can be lifesaving. Use in the first 7 days can be detrimental and needs to be limited to life threatening illness in that period.
- Promethazine is the antihistamine of choice in Type 1 hypersensitivity reactions. It can suppress all the immediate manifestations of Type 1 reactions rapidly and effectively. H2 antagonists may need to be added in those with gastrointestinal symptoms.
- Montelukast, a leukotriene receptor antagonist, blocks the effects of cysteinyl leukotrienes, a unique feature not achieved by corticosteroids. It has both bronchodilator and anti-inflammatory activity. It is indicated in the prophylaxis and treatment of atopic conditions, and has benefit in preventing Type 1 reactions.
- Beclometasone is an inhaled steroid that can suppress lung inflammation topically. It would be beneficial in patients with prolonged reactions with associated dry cough. It could also limit lung fibrosis and progression to COPD.

Other less common drugs that should have benefit are: ipratropium bromide / sodium chromoglycate/ ketotifen.

Protocol

Viral phase

Mild symptoms: Sore throat, loss of smell etc.

- Hydroxychloroquine 200mg dly x 5 days
- Montelukast 10mg dly x 1 month
- Symptomatic treatment
- Moderate symptoms: Present later into illness so enquire about day of onset of symptoms - dry cough, mucopurulent bronchitis etc.
- Hydroxychloroquine 200mg dly x 5 days
- Azithromycin 500mg on day 1, then 250mg dly for 4 more days, or other more appropriate antibiotic
- Montelukast 10mg dly x 1 month
- Symptomatic treatment

Most patients recover quickly from mild symptoms. Those with moderate symptoms take a little longer.

All patients should be educated to be aware of new symptoms from day 7 onwards, even if completely well, and report immediately for treatment. These symptoms are usually: generalised body aches and pains, fatigue, dyspnoea and decreasing SpO_2. These herald the start of the hypersensitivity reaction.

Hypersensitivity phase

Range of presentation: rapidly progressive dyspnoea with SpO_2 low 80% with or without chest symptoms to slow prolonged SpO_2 decrease, prolonged cough, wheeze etc.

- Prednisone 50mg stat and decrease single dly morning dose by 5mg over next 9 days...50, 45, 40, 35mg mane... Those who present with mild prolonged symptoms may need lower doses tapered over a longer period.
- Promethazine 25mg stat then tds x 5 days.
- Adrenaline nebs stat if severe dyspnoea or if hypotension suspected
- Aspirin prophylaxis mane x 1 month.
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- Naproxen 250mg bd for fever, as it is from allergic inflammation, not infection. Paracetamol not effective alone.
- Beclate 200mcg inhaler bd for those with chronic dry cough (Topical steroid)
- Sodium Chromoglycate/ Ketotifen/ Ipratropium bromide inhaler may give better results and possible prophylactic benefit

Future infections

Patients who do not develop a hypersensitivity reaction during the initial infection are either previously unexposed, or tolerant. Specific IgE screening would identify those at risk of subsequent reactions, and significantly elevated levels of IgE would identify those prone to severe reactions. Montelukast would prevent these reactions and should be used prophylactically in those with elevated IgE levels.

Observations

The following are my personal observations based on the examination of over 200 COVID patients, from presentation to full recovery, using the above treatment protocol. Many observations confirm the existence of a Type 1 hypersensitivity reaction.

Hydroxychloroquine and doxycycline

Hydroxychloroquine initiated early helps symptomatically and can suppress the hypersensitivity reaction on day 7. It is however less effective than other drugs in modulating immune hypersensitivity when started later on in the illness.

Doxycycline has been used prophylactically in a large group (160) of high-risk individuals (teachers and police) over the past three months. Fewer individuals in the prophylaxis group have so far become infected, compared to their colleagues.

The four individuals that became infected had none to mild transient symptoms that resolved spontaneously during the viral phase. They were home isolated, with none of their close contacts testing positive or exhibiting symptoms over the duration of their illness. This may be indication of doxycycline's suppressive effect on viral replication and consequently on viral transmission. However, three went on to develop dyspnoea on day 7 that resolved rapidly with treatment. Evaluation is ongoing.

All the other drugs used were dictated by bacterial infections and presenting symptoms, with their benefits reasonably obvious.

Patients presenting with dyspnoea or decreased SpO_2 after day 7 were immediately started on treatment as outlined. All had improvement in symptoms and SpO_2 within 24 hours. The most telling was a group of the 12 most hypoxic patients, who all presented after day 7, with SpO_2 in the low 80%, all having severe dyspnoea etc. Every one of them had symptomatic relief within a few hours and returned to >96% SpO_2 within 24 to 36 hours of starting treatment. This was achieved with outpatient treatment, on Room Air without the need for oxygen, and all 12 made full recoveries in a few days.

Montelukast, prednisone and promethazine

All patients started on montelukast in the first 7 days had no reaction on day 7 or thereafter. (About 80 symptomatic patients)

Promethazine effectively cleared chemical mediators, thus preventing lung damage and the resultant cytokine release, giving rapid relief from dyspnoea.

Prednisone, promethazine and montelukast proved to be lifesaving, and after seeing over 200 COVID patients and counting, we have not had a death, nor hospitalisation of a patient. All recovered completely within 14 days from onset.

No other medications in current use for the treatment of COVID 19 ie, remdesivir, tocilizumab, convalescent plasma etc, have shown such rapid response and predictable outcome in severely ill patients, negating the need for oxygen and hospitalisation.

Implications of observations

The rapid response to the medications used to treat Type 1 hypersensitivity reactions confirms its existence. This could have some serious implications for the future management of the COVID pandemic.

Monitoring for a hypersensitivity reaction and prompt treatment would decrease morbidity and mortality significantly. Those with mild to moderate initial illness will develop tolerance with subsequent exposure. However, those that were initially asymptomatic due to it being their first exposure, will become sensitised, and run the risk of subsequent reactions.

Identifying the specific IgE involved in this reaction and quantifying its levels would help identify those at risk. This would also help predict the severity of reaction to future exposure, and guide prophylactic and preventive treatment.

Vaccines against the virus would only benefit those that are hypersensitive, and blanket vaccinations would be unnecessary and unsafe in view of the rush to bring it to market without long term evaluation. Being able to identify hypersensitive individuals and provide appropriate information and treatment may negate the need for a vaccine altogether.

Conclusion

With the high mortality and morbidity from COVID 19, it is my wish that the information presented above will help save lives and guide further research and management. The protocol and its deficiencies provide a valuable starting point for further evaluation of treatment interventions. I hope this brings some clarity during this difficult time.

lead to a pneumonia with associated dyspnoea.

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The four individuals that became infected had none to mild transient symptoms that resolved spontaneously during the viral phase. They were home isolated, with none of their close contacts testing positive or exhibiting symptoms over the duration of their illness. This may be indication of doxycycline's suppressive effect on viral replication and consequently on viral transmission. However, three went on to develop dyspnoea on day 7 that resolved rapidly with treatment. Evaluation is ongoing.

All the other drugs used were dictated by bacterial infections and presenting symptoms, with their benefits reasonably obvious.

Patients presenting with dyspnoea or decreased SpO_2 after day 7 were immediately started on treatment as outlined. All had improvement in symptoms and SpO_2 within 24 hours. The most telling was a group of the 12 most hypoxic patients, who all presented after day 7, with SpO_2 in the low 80%, all having severe dyspnoea etc. Every one of them had symptomatic relief within a few hours and returned to >96% SpO_2 within 24 to 36 hours of starting treatment. This was achieved with outpatient treatment, on Room Air without the need for oxygen, and all 12 made full recoveries in a few days.

Montelukast, prednisone and promethazine

All patients started on montelukast in the first 7 days had no reaction on day 7 or thereafter. (About 80 symptomatic patients)

Promethazine effectively cleared chemical mediators, thus preventing lung damage and the resultant cytokine release, giving rapid relief from dyspnoea.

Prednisone, promethazine and montelukast proved to be lifesaving, and after seeing over 200 COVID patients and counting, we have not had a death, nor hospitalisation of a patient. All recovered completely within 14 days from onset.

No other medications in current use for the treatment of COVID 19 ie, remdesivir, tocilizumab, convalescent plasma etc, have shown such rapid response and predictable outcome in severely ill patients, negating the need for oxygen and hospitalisation.

Implications of observations

The rapid response to the medications used to treat Type 1 hypersensitivity reactions confirms its existence. This could have some serious implications for the future management of the COVID pandemic.

Monitoring for a hypersensitivity reaction and prompt treatment would decrease morbidity and mortality significantly. Those with mild to moderate initial illness will develop tolerance with subsequent exposure. However, those that were initially asymptomatic due to it being their first exposure, will become sensitised, and run the risk of subsequent reactions.

Identifying the specific IgE involved in this reaction and quantifying its levels would help identify those at risk. This would also help predict the severity of reaction to future exposure, and guide prophylactic and preventive treatment.

Vaccines against the virus would only benefit those that are hypersensitive, and blanket vaccinations would be unnecessary and unsafe in view of the rush to bring it to market without long term evaluation. Being able to identify hypersensitive individuals and provide appropriate information and treatment may negate the need for a vaccine altogether.

Conclusion

With the high mortality and morbidity from COVID 19, it is my wish that the information presented above will help save lives and guide further research and management. The protocol and its deficiencies provide a valuable starting point for further evaluation of treatment interventions. I hope this brings some clarity during this difficult time.